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Quality-adjusted survival analysis shows differences in outcome after immunosuppression or bone marrow transplantation in aplastic anemia

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Abstract Bone marrow transplantation (BMT) and immunosuppression (IS) have improved the prognosis of aplastic anemia; both treatments have specific advantages and drawbacks but similar survival rates. Analysis of additional endpoints may help in treatment decisions. In a single-center study, patients with aplastic anemia treated with IS ($n=155$) or BMT ($n=52$) were compared for survival, event-free survival, and quality-adjusted time without symptoms and toxicity (Q-TWiST). Probability of overall and event-free survival at 15 years was similar among both groups (BMT $51\pm 15\%$ and $25\pm 14\%$, IS $53\pm 10\%$ and $27\pm 8\%$), with more early deaths in the transplant group and more late deaths in the IS group. There were differences in terms of mean duration of seven analyzed health states: time with symptoms from treatment-related toxicity (IS 0.36 years, BMT 0.27), transfusion dependency (IS 0.66 years, BMT 0.1 years), partial remission (IS 3.27 years, BMT 1.42), and secondary clonal disorder (IS 0.68 years, BMT 0.04) was significantly longer for IS compared to BMT ($p\leq 0.001$). Patients treated with BMT spent more time with extensive chronic graft-versus-host disease (GvHD) (IS 0 years, BMT 0.96, $p<0.023$) and in CR without drugs (IS 1.22 years, BMT 2.43, $p=0.056$). In conclusion, survival, event-free survival, and Q-TWiST are similar. BMT-treated patients had

longer periods free from symptoms, while IS-treated patients needed closer medical care, transfusion support, and medications.

Keywords Aplastic anemia · Treatment decisions · Quality of life

Introduction

Severe aplastic anemia is a rare disease characterized by pancytopenia and bone marrow aplasia. The goal of the treatment is to improve peripheral blood counts in order to free the patients of transfusions and the risk of bleeding and opportunistic infections. Bone marrow transplantation (BMT) as well as immunosuppression are standard treatment modalities that have improved the previously poor prognosis [1–6]. After any of the two treatments, more than 80% of patients are free from transfusions and some of them even normalize their cell counts. BMT is the standard approach for younger patients with an HLA-matched sibling donor, while immunosuppression is the treatment of choice for patients not eligible for BMT. In patients over the age of 40, it is less clear whether they should receive a BMT or antithymocyte globulin (ATG) even if they do have a matched sibling donor. With BMT, the defective organ is replaced by healthy marrow. Immunosuppressive treatment on the other hand will not cure the disease. It aims at eliminating “autoaggressive” cells that are responsible for the aplastic marrow resulting in pancytopenia. Despite these differences, there is no clear-cut advantage in terms of overall survival for either treatment form. Each treatment modality has its advantages and drawbacks [7–12].

Overall survival does not sufficiently describe the outcomes of patients with aplastic anemia. Therefore, one might want to take additional endpoints such as event-free survival, the ability to tolerate treatment, and quality of life during different sequences of relevant health states into account in the decision making process, when different treatment options result in similar long-term

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survival. In aplastic anemia, quality of life outcomes are affected by treatment toxicity, graft rejection, infections, and graft-versus-host disease (GvHD) after BMT [13–15], and by persisting cytopenia due to slow or incomplete responses, relapse of aplastic anemia, or the development of clonal disorders such as myelodysplastic syndrome (MDS) or paroxysmal nocturnal hemoglobinuria (PNH) after immunosuppression [16–18].

In order to integrate quality of life considerations into comparing the two treatment modalities, additional factors such as treatment toxicity, transfusion and drug requirement, chronic GvHD, or clonal evolution have to be considered. The quality-adjusted time without symptoms and toxicity (Q-TWiST) methodology splits up survival times into several distinct periods associated with relevant health states weighted by quality of life factors [19–23]. We compared in a retrospective, single-center study aplastic anemia patients treated with BMT to those treated with immunosuppression applying survival, event-free survival, and Q-TWiST methodology.

Patients and methods

Study population

Patients with aplastic anemia as defined by the criteria of Bacigalupo and Camitta [24, 25] were treated since 1976 in a prospective single-center study at the University Hospital of Basel. Patients younger than 40 years of age with an HLA-matched sibling donor received allogeneic

BMT, older patients and patients without a marrow donor were treated with ATG-based immunosuppression. On 1 January 1999, 207 patients were included in the study. Fifty-two underwent marrow transplantation and 155 received ATG. Of the 155 patients receiving ATG as first-line treatment, 8 were subsequently transplanted. These eight patients are included in the ATG group.

The characteristics of the patients are shown in Table 1. Of the 207 patients, 55 fulfilled the criteria of very severe aplastic anemia, 88 had severe, and 64 patients non-severe aplastic anemia. Patients with non-severe aplastic anemia had either thrombocytes $<10 \times 10^9 \text{ l}^{-1}$, or neutrophils $<0.5 \times 10^9 \text{ l}^{-1}$, or depended on transfusions. Both treatment groups were comparable for gender, etiology, severity of the disease, and for blood values before first-line treatment. The median age at first-line treatment was 19 years (range: 2–55 years) for BMT compared to 23 years (range: 2–74 years) in ATG-treated patients ($p=0.039$). The difference in frequency of splenectomy is due to a protocol of splenectomy in nonresponders to ATG prior to salvage immunosuppressive retreatment [26]. All patients were either treated in laminar air flow rooms or in single rooms with reverse isolation. They all received standard supportive care, including transfusions of red blood cells and single-donor platelet concentrates, as well as application of broad-spectrum intravenous antibiotics in case of fever or infections. The median duration of observation since first-line treatment in surviving patients was similar in both treatment groups, i.e., 11.5 years (range: 2–22 years) for BMT patients and 11.3 (range: 0.2–22 years) for patients treated with ATG.

Table 1 Characteristics of the patients with aplastic anemia treated with bone marrow transplantation (BMT) or antithymocyte globulin (ATG)

	BMT	ATG	<i>p</i> value
Patients(<i>n</i>)	52	155	
Male gender	27 (52%)	85 (55%)	0.418
Age at first treatment			
Median age (range) (years)	19 (2–55)	23 (2–74)	0.039
Patients >40 years	3 (6%)	37 (24%)	0.047
Etiology			
Idiopathic	42 (81%)	125 (81)	0.828
Viral	3 (6%)	10 (6%)	
Toxic/drugs	7 (13%)	18 (12)	
Others	0 (0%)	2 (1%)	
Severity of aplastic anemia ^a			
Non-severe	14 (27%)	50 (32%)	0.759
Severe	23 (44%)	65 (42%)	
Very severe	15 (29%)	40 (26%)	
Median blood values at diagnosis (range)			
Neutrophil counts ($\times 10^9 \text{ l}^{-1}$)	0.45 (0–3.0)	0.46 (0–2.1)	0.536
Platelet counts ($\times 10^9 \text{ l}^{-1}$)	14 (1–97)	15 (1–218)	0.450
Reticulocyte counts ($\times 10^9 \text{ l}^{-1}$)	14 (0–77)	18 (0–186)	0.384
MCV (fl)	96 (84–126)	97 (80–133)	0.948
Transfusion dependence	51 (98%)	141 (91%)	0.78
Splenectomy	2 (4%)	84 (54%)	<0.001
Median time interval (range)			
Diagnosis first-line treatment (months)	1.7 (0.2–14)	1.2 (0.03–378)	0.130
Follow-up (years)	11.5 (2–22)	11.3 (0.2–22)	0.439

^aAccording to Bacigalupo et al. [24], Camitta et al. [25]

Treatment protocol

The treatment protocol and overall results of the study have been published previously [27–29]. In short, the ATG treatment protocol was as follows: from 1976 to 1991 equine antithymocyte globulin from the same manufacturer (Lymphoser, Swiss Serum and Vaccine Institute, Berne, Switzerland) was used in a dose of 40 mg/kg per day for 4 days. Since 1992 a different equine antithymocyte globulin preparation (Lymphoglobuline), provided by SangStat (Fremont, Calif., USA), was used in a dose of 15 mg/kg per day for 5 days. Methylprednisolone was given in a dose of 1 g/day for all patients treated between 1981 and 1992 and in a dose of 2 mg/kg per day thereafter. Cyclosporine in a dose of 5 mg/kg per day was added to the regimen in 1991 and continued for at least 1 year.

All patients treated with BMT were conditioned with cyclophosphamide at a dose of 50 mg/kg per day for 4 days. Twenty-one patients received unirradiated donor buffy coat after transplantation. Since 1994, ATG was added at a dose of 30 mg/kg daily for 3 days (Lymphoglobuline, SangStat, Fremont, Calif., USA). For prevention of GvHD patients received methotrexate alone until 1979. Since July 1979, patients were given cyclosporin A, and since 1990 a combined regimen of methotrexate and cyclosporine was applied except for children, who continued to receive cyclosporine alone. Bone marrow was used as a source of stem cells in 51 of the 52 transplanted patients and peripheral stem cells in one. The donor was an HLA-identical sibling in 51 and a syngeneic donor in one patient.

Data analysis and definitions

A detailed review of all patient charts was the basis of this report. Variables analyzed included disease-related information, treatment (first-line and subsequent), time to response, time to a first event, and time to death or last follow-up. Clinical state (transfusions and medication after first-line treatment) and biological investigations [blood counts, bone marrow examination, screening tests for PNH, including hemosiderin in the urine, Ham's (acid hemolysin), and sucrose test] were measured before, 3, 6, and 12 months after first-line treatment, and then annually until last follow-up.

Response to treatment was defined as follows: complete remission (CR): neutrophil counts $\geq 1.5 \times 10^9 \text{ l}^{-1}$, hemoglobin $\geq 120 \text{ g/l}$, and platelet counts $\geq 150 \times 10^9 \text{ l}^{-1}$; partial remission: patients not fulfilling the criteria of CR, but achieving transfusion independence; nonresponse: patients who never fulfilled criteria of complete or partial remission, died from aplasia, or needed a second-line treatment before fulfilling criteria of partial or complete remission. An event was defined as nonresponse, relapse of aplastic anemia, development of a clinically relevant clonal complication such as MDS, PNH, or solid tumor, extensive chronic GvHD, or death. Criteria for late clonal transformation have been published in detail [30]. Labo-

ratory signs of PNH without clinical manifestation, limited chronic GvHD, and silent nonmalignant tumors (liver adenomas) were not considered as an event.

Causes of death were subdivided into disease-related deaths, treatment-related deaths, event-related deaths, and deaths independent from disease or treatment. Bleeding and infections were considered disease related as long as they occurred during the aplastic phase. For ATG patients, death was treatment related when it occurred during or immediately after ATG infusion. For transplanted patients, treatment-related deaths included deaths due to toxicity, acute GvHD, infections occurring after hemopoietic regeneration, interstitial pneumonia, and early graft rejection. Death occurring after relapse, late graft rejection, MDS, PNH, or solid tumors were classified as event-related deaths. In all other cases, the cause of death was classified as not related to aplastic anemia or its treatment.

Statistical analysis

The chi-square test was used for comparisons of categorical data and the Mann–Whitney U test for continuous unrelated variables among groups. Survival probabilities were estimated using the Kaplan–Meier method [31]. The log-rank test was used to compare survival [32]. Outcomes analyzed between BMT- and ATG-treated patients were overall survival, event-free survival (considering death, extensive chronic GvHD, secondary malignancy, MDS or clinical PNH, and nonresponse to treatment or relapse of aplastic anemia as events), and quality-adjusted survival.

The Q-TWiST is based on subdividing survival times in distinct successive time lengths of relevant health states. For comparison of two cancer treatment strategies usually three states are defined, time with treatment-related toxicity, time without symptoms and toxicity (TWiST), and time from treatment failure to death [33, 34]. In aplastic anemia the situation is more complex. We defined the following clinically relevant health states (Table 2): the time in treatment-related toxicity (TOX) was arbitrarily fixed for patients of both treatment groups and for each treatment course to 3 months. TWiST was the time an individual spent in complete remission, free from medication, and without an event, as described above. The other relevant health states were time with clonal disease (CLON), time with extensive chronic GvHD (GvHD), time with transfusion dependency (TRANS), time with partial remission (PR), or time with complete remission but still on medication (CR). A hierarchy of the different health states was established in case a patient was in two health states at the same time. Accordingly, time with CLON stood over all other health states. After that came in the following order: time with GvHD, time with TRANS, time with PR, time with CR, and finally time with TWiST. A utility factor was allocated to each health state varying on a scale from 0 (as bad as death) to 1 (TWiST) to reflect the health state's quality of life value relative to time in TWiST. The utility coefficient (μ) was defined for TWiST

as 1, for CR and PR as 0.75, for TOX as 0.25, and for all other states as 0.5. The weighting of the utility factor was based on the 30 years of clinical experience of the study center and was done like the weighting of the original groups of Q-TWiST. Mean Q-TWiST for each treatment modality was then calculated from the mean clinical health state duration as

Q – TWiST

$$= [\mu_{\text{TOX}} \times \text{TOX}] + [\text{TWiST}] + [\mu_{\text{CLON}} \times \text{CLON}] \\ + [\mu_{\text{GvHD}} \times \text{GvHD}] + [\mu_{\text{TRANS}} \times \text{TRANS}] \\ + [\mu_{\text{PR}} \times \text{PR}] + [\mu_{\text{CR}} \times \text{CR}]$$

where μ_{TOX} is the utility coefficient for toxicity, μ_{CLON} for clonal complications, μ_{GvHD} for chronic GvHD, μ_{TRANS} for transfusion dependency, μ_{PR} for partial remission, and μ_{CR} for complete remission but still with drugs.

A threshold utility analysis comparing BMT with ATG treatment was performed for PR (U_{PR}), which was the most relevant health state in terms of duration and differences between treatment groups. The threshold utility analysis was calculated for all possible values ranging from 0.0 to 1.0 (Fig. 2). Finally, Kaplan–Meier estimates for the time to events that signal transitions between clinical health states were used to partition the area under the overall survival curves separately for each treatment modality [35].

Results

Survival and event-free survival

At the time of last follow-up, 122 of 207 patients [59%; 95% confidence interval (CI) 52–65%] were alive and 85 (41%; 95% CI 34–48%) had died, 24 (46%; 95% CI 32–62%) after BMT and 61 (39%; 95% CI 32–47%) after ATG treatment ($p=0.241$). The probability of survival at 15 years was statistically similar between both treatment groups; it was $51 \pm 15\%$ after transplantation and $53 \pm 10\%$

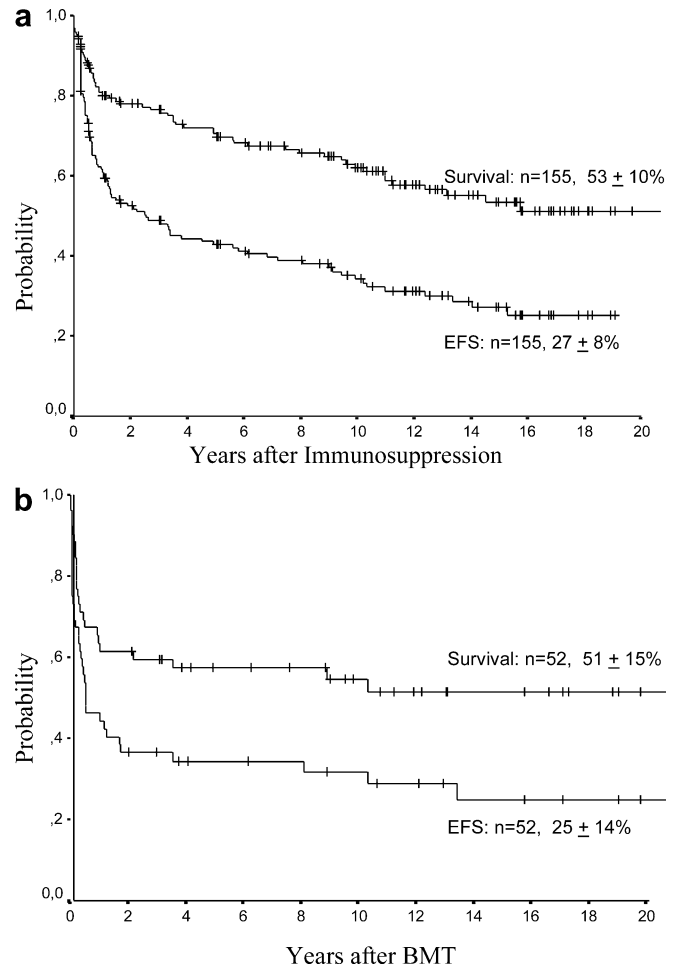


Fig. 1 **a** Actuarial survival and event-free survival (EFS) at 15 years according to Kaplan–Meier among 155 patients with aplastic anemia treated with ATG. **b** Actuarial survival and event-free survival (EFS) at 15 years according to Kaplan–Meier among 52 patients with aplastic anemia treated with BMT

after ATG ($p=0.20$), with more early deaths in the transplant group and more late deaths in the immunosuppression group (Fig. 1). There was an improvement in

Table 2 Definitions and criteria of health states for Q-TWiST analysis. *MDS* myelodysplastic syndrome, *PNH* paroxysmal nocturnal hemoglobinuria, *GvHD* graft-versus-host disease

Name	Definition	Criteria	Utility coefficient
TwIST	Time without symptoms and toxicity (and without drugs)	Time in complete remission, without drugs, transfusions, clonal disease, without extended GvHD, and not in toxicity phase	1
TOX	Toxicity	Initial period of treatment, arbitrarily fixed for each course to 3 months	0.25
TRANS	Time with transfusion dependency	Time with transfusion dependency, but without clonal disease or extended GvHD, and not in toxicity phase	0.5
PR	Time in partial remission	Time not in complete remission, but without transfusion dependency, clonal disease, or extensive GvHD, and not in toxicity phase	0.75
CR	Time in complete remission	Time in complete remission, but still receiving drug medication, without clonal disease, without extended GvHD, and not in toxicity phase	0.75
GvHD	Time with extensive GvHD	Time with extensive chronic GvHD, but not in toxicity phase	0.5
CLON	Time with clonal disease	Time with a clonal disease, such as MDS, PNH, or solid tumor	0.5

survival probabilities by decade for both treatment groups with probabilities at 5 years before 1980 of $40 \pm 22\%$ (BMT) and $55 \pm 18\%$ (ATG), between 1980 and 1990 of $60 \pm 22\%$ (BMT) and $74 \pm 9\%$ (ATG), and after 1990 of $83 \pm 21\%$ (BMT) and $75 \pm 18\%$ (ATG). This improvement by decade was statistically significant for the transplanted patients ($p=0.05$), but not for the ATG-treated group ($p=0.1$). The event-free survival at 15 years was similar between both treatment groups ($p=0.12$), with $25 \pm 14\%$ after BMT and $27 \pm 8\%$ after ATG treatment (Fig. 1).

Events and causes of death

Frequency and causes of events and deaths are listed in Table 3. Fifty-three events were observed in 52 patients treated with BMT and 196 events in 155 patients treated with ATG. Of the 52 patients treated with BMT, 21 patients had one and 16 patients two events. Of the 155 patients treated with ATG, 34 patients had one, 39 patients two, and 23 patients three or more events. During the study period, 15 of 52 (29%) BMT-treated and 59 of 155 (38%) ATG-treated patients never had an event. The overall frequency of events was not different between patients treated with BMT and ATG ($p=0.302$). However, there were differences in the type of an event between both groups. Primary refractory disease occurred significantly more often after immunosuppression (41 of 196 events, 21% vs 5 of 53 events, 9%, $p=0.087$), and MDS or leukemia (21 of 196, 11%, $p=0.009$) or PNH (18 of 196, 9%, $p=0.016$) were observed only after immunosuppression. Extensive chronic GvHD was observed only after BMT (12 of 53, 23%, $p<0.001$). There was no difference in the frequency of relapse/rejection or the occurrence of a solid tumor between both treatment groups. There were clear differences in cause of death between both groups (Table 3). Major cause of death in BMT patients was treatment related (46%), followed by disease-related deaths (33%). In contrast, after ATG treatment, the major cause of death was either disease related (41%) or event related (41%). Deaths due to toxicity were less frequent than in BMT patients (Table 3).

Q-TWiST analysis

The mean observation time per patient did not differ between the treatment groups. It was 6.41 years for transplanted patients and 7.80 years for ATG-treated patients ($p=0.181$). Important differences were found between both treatment modalities in terms of mean duration of various health states (Table 4). The mean time per patient spent with toxicity (ATG 0.36 years, BMT 0.27 years), with transfusion dependency (ATG 0.66 years, BMT 0.1 years), with partial remission (ATG 3.27 years, BMT 1.42 years), and with a clonal disorder (ATG 0.68 years, BMT 0.04 years) was significantly longer for ATG-treated patients compared to patients treated with BMT ($p \leq 0.001$). The difference in time spent with toxicity is

Table 3 Frequency and type of events, as well as causes of deaths in patients treated with bone marrow transplantation (BMT) or antithymocyte globulin (ATG)

	BMT, <i>n</i> =52	ATG, <i>n</i> =155	<i>p</i> value
Patients with an event	37 (71%)	96 (62%)	0.302
With a single event	21 (40%)	34 (22%)	
With two events	16 (31%)	39 (25%)	
With three events	0 (0%)	23 (15%)	
Number/type of events	53	196	
Primary refractory	5 (9%)	41 (21%)	0.087
Relapse/late rejection	10 (19%)	50 (26%)	0.411
MDS/leukemia	0 (0%)	21 (11%)	0.009
Clinical PNH ^a	0 (0%)	18 (9%)	0.016
Extensive chronic GvHD ^b	12 (23%)	0 (0%)	<0.001
Malignant tumor ^c	1 (2%)	5 (2%)	1.0
Death	24 (45%)	61 (31%)	0.077
Others	1 (2%)	0 (0%)	0.213
Number/type of deaths	24 (46%)	61 (39%)	0.241
Treatment-related deaths	11 (46%)	8 (13%)	0.003
Early rejection	3	1 ^d	
Acute GvHD	7	0	
Toxic	1	7	
Disease-related deaths	8 (33%)	25 (41%)	0.686
Bleeding	1	14	
Infection	7	11	
Event-related deaths	3 (13%)	25 (41%)	0.024
Chronic GvHD	3	0	
MDS or leukemia	0	13	
PNH	0	2	
Relapse of aplastic anemia	0	9	
Solid tumor	0	1	
Death without evident association	2 (8%)	3 (5%)	0.618
Car accident	1	1	
Heart disease	1	1	
Unknown	0	1	

^aBiological paroxysmal nocturnal hemoglobinuria not included ($n=12$)

^bLocalized cutaneous or mucosal chronic GvHD not included ($n=5$)

^cBenign tumors not included ($n=3$ liver adenomas)

^dAfter secondary bone marrow transplantation

explained by the larger proportion of patients requiring retreatment in the ATG group. In contrast, patients treated with BMT spent more time with extensive chronic GvHD (0.96 years for BMT vs 0 for ATG, $p<0.023$) and in TWiST (BMT 2.43 years, ATG 1.22 years, $p=0.056$). None of the eight patients receiving ATG as a first-line treatment developed chronic GvHD after a subsequent transplant. The time spent in complete remission but still receiving medication was not statistically different between both groups, with 1.21 years for BMT and 1.60 years for ATG ($p=0.431$). Using the utility factors chosen previously, the Q-TWiST times were similar for the two treatment groups, i.e., 5.08 years after BMT and 5.72 years after ATG treatment ($\Delta -0.64$, 95% CI -2.25 to $+0.97$, $p=0.434$). In terms of relative duration, there are

Table 4 Quality-adjusted time without symptoms and toxicity (Q-TWiST) and drugs of patients with aplastic anemia treated with bone marrow transplantation (BMT) or antithymocyte globulin (ATG)

Time interval	BMT		ATG		Δ Between BMT and ATG		
	Mean years per patient (%)	Total years	Mean years per patient (%)	Total years	Mean years per patient	95% CI	<i>p</i> value
Total years	6.41	333.5	7.80	1,207.5	-1.38	-3.40/+0.65	0.181
TWiST	2.43 (38%)	126.3	1.22 (16%)	189.3	+0.21	+0.33/+2.45	0.056
TOX	0.27 (4%)	14.3	0.36 (4%)	55.8	-0.09	-0.12/-0.05	<0.001
TRANS	0.10 (1%)	4.8	0.66 (8%)	102.8	-0.57	-0.80/-0.35	<0.001
PR	1.42 (22%)	73.8	3.27 (42%)	507.0	-1.85	-2.93/-0.78	0.001
CR with drugs	1.21 (19%)	63.0	1.60 (20%)	248.3	-0.40	-1.37/+0.59	0.431
GvHD	0.96 (15%)	50.0	0	—	+0.96	+0.14/+1.78	0.023
CLON	0.04 (1%)	2.0	0.68 (9%)	104.5	-0.64	-0.88/-0.39	<0.001
Q-TWiST ^c	5.08	264.3	5.72	887.2	-0.064	-2.25/+0.97	0.434

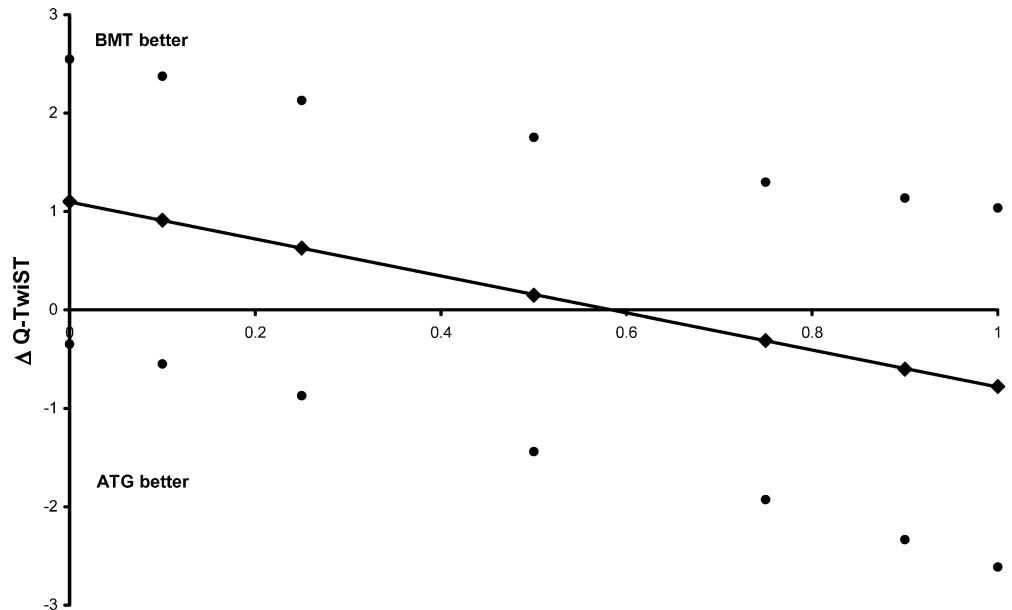
considerable differences between the health states: BMT patients spent for instance 38% of their time in TWiST and 19% in PR compared to 16% and 42%, respectively, for ATG-treated patients (Table 3).

The threshold analysis of the PR utility factor is presented in Fig. 2. PR is the health state with the largest difference between the BMT and ATG groups. The plot illustrates the mean difference in Q-TWiST between BMT and ATG by varying the U_{PR} between 0 and 1. Irrespective of utility factor attributed to PR, there is no significant difference in Q-TWiST among both groups. Figure 3 shows the partitioning of survival times for each treatment group into the four clinically most relevant health states: TOX (including time with toxicity and time with transfusion dependency), PR (including time in partial remission and time in complete remission but requiring drugs), CLON for ATG group or GvHD for BMT group (including extensive GvHD and clonal complications), and TWiST.

Discussion

BMT and immunosuppression are both effective treatment modalities for patients with aplastic anemia and 15-year survival probabilities are similar. More early deaths were observed in the transplant group and more late deaths in the ATG group. Event-free survival is an outcome measure that reflects the probability of a patient being alive without complications due to disease or treatment. This outcome measure has rarely been used in previous publications of aplastic anemia [36]. There were no significant differences in event-free survival at 15 years after BMT and ATG treatment. However, there were significant differences in outcomes affecting the quality of life of these patients. The Q-TWiST analysis allows for a comparison of the time period spent in different health states when overall survival does not show a preference between the two treatment modalities. The quality-adjusted time without symptoms, toxicity and drugs is similar after BMT and ATG treatment, but both treatment modalities differ in

Fig. 2 Threshold utility analysis was performed for the period “partial remission” (PR). The plot of mean difference in Q-TWiST between BMT- and ATG-treated patients using a utility factor (U_{PR}) between 0 and 1 is illustrated. The points on each side of the line representing the mean difference in Q-TWiST are the 95% confidence intervals



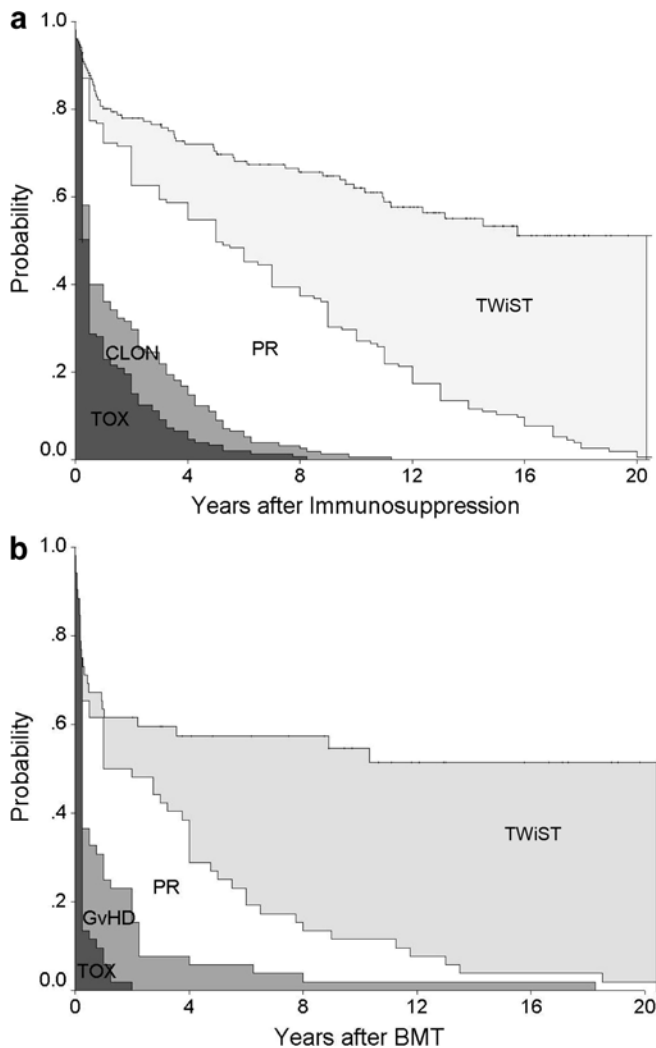


Fig. 3 **a** Partitioning of survival time for patients treated with ATG into the four clinically most relevant health states: TOX (including time with toxicity and time with transfusion dependency), PR (including time in partial remission and time in complete remission but necessitating drugs), CLON (including clonal complications), and TWiST. **b** Partitioning of survival times for patients treated with bone marrow transplantation into the four clinically most relevant health states: TOX (including time with toxicity and time with transfusion dependency), PR (including time in partial remission and time in complete remission but necessitating drugs), GvHD (including extensive GvHD and clonal complications), and TWiST

time periods spent in various health states. ATG-treated patients spent more time requiring transfusions and drugs, endure longer periods with abnormal blood values, and have a higher risk of clonal disorder. Patients in the ATG group required additional treatment more frequently than BMT patients due to more relapses and a higher incidence of refractory disease. In contrast, BMT patients spent nearly 60% of their time without symptoms and toxicity (in TWiST and CR with drugs).

The implications of these findings must be considered in the context of benefits of treatment over time. Although overall survival, event-free survival, or Q-TWiST do not favor one of the two treatments, BMT patients spent more time free from any medication and without symptoms of

the disease and toxicity. In contrast, ATG patients spent more time in health states other than TWiST and therefore had greater requirements for close medical care, transfusion support, and medication. Our results suggest that ATG patients spend more time with a reduced quality of life, and by spending more time in cost-intensive health states are likely to produce more costs due to medical care.

There is no patient-derived information available to indicate the appropriate utility factors for health states such as toxicity, transfusions, clonal disorders, GvHD, or partial remission. In our view, patients in partial remission have a fairly good quality of life, restricted by medications and frequent doctor visits; therefore, the coefficient of 0.75 was chosen for these periods, whereas for periods spent with transfusion requirements, extensive chronic GvHD, or clonal complications a coefficient of 0.5 was chosen reflecting considerable impairment of quality of life. A coefficient of 0.75 was chosen for the time spent in complete remission but still requiring regular medication, because taking drugs on a daily basis clearly interferes with quality of life. Yet different weighting of the utility coefficients might affect the results of the Q-TWiST analysis. Therefore, a threshold utility analysis was performed for the most relevant health states in terms of duration and differences between treatment groups. With this, we show that varying the utility factors for PR does not affect the results of the Q-TWiST analysis.

There are limitations to this study. Patients receiving immunosuppression were by study design significantly older. Therefore, we cannot exclude that age disparity could play a role in some of the differences observed between treatment groups. Furthermore, definitions of transition periods were arbitrary. There is heterogeneity in some of the transition periods; for instance, the time spent in partial remission includes patients who have close to normal blood counts and patients whose hemopoiesis is just sufficient to keep them free of transfusions. During the time spent in PR, more transplanted patients have nearly normal blood values, while ATG patients are more likely to present lower blood counts. In addition, the study period covers almost 3 decades. During the whole study period, changes in the protocols and progress in supportive care and treatment modalities have led to improvement of survival and event-free survival. However, there was no difference in Q-TWiST when comparing ATG-treated patients and patients treated with BMT (results not shown) by decade. Finally, Q-TWiST analysis attempts to provide information on quality of life without direct patient-centered questionnaires. Such an evaluation is easily performed in a study covering a limited time period [37]. A Q-TWiST evaluation is much more critical in studies with chronic disorders, such as aplastic anemia, where the longest observation time exceeds 20 years and the history of an individual patient is often complex [37, 38].

Even with these limitations, the Q-TWiST analysis is a methodology that allows evaluating retrospectively the time a patient spent at different health states, assuming that quality of life is dependant on each particular health state [39], and gives us a complementary view on the outcome

of the two standard treatment modalities. Despite similar survival and event-free survival probabilities, patients treated with BMT spend more time cured from their disease, while ATG-treated patients have greater requirements for close medical care, transfusion support, and medications and spend therefore more time in cost-intensive intervals. The results presented should be helpful for patient information and making decisions for patients with aplastic anemia.

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